REMARKS

I. Preliminary Remarks

The present invention is directed to a method for the identification/isolation of modulators of secretase activity. While there exist various methods in the prior art for screening for secretase modulators there remains a need in the art for improved in vivo screening systems for the identification of such modulators.

According to the invention, eukaryotic host cells are produced which comprise a) a fusion protein comprising a secretory protein, a membrane anchor domain and a secretase cleavage sequence, b) a protein comprising a secretase activity recognizing the cleavage sequence of the fusion protein and c) at least one reporter gene under control of a transcriptional activation system which is regulated by the release of the secretory protein from the fusion protein by the secretase activity and its subsequent secretion. These cells are contacted with a test substance and then cultured under suitable conditions such that the reporter gene allowing detection and/or survival of the cells is only expressed or repressed in a manner that is dependent on an altered secretase activity due to the test substance. The reporter gene is chosen such that it is under control of a transcription activation system that is regulated not just by the release of the secretory protein from the fusion protein but also by the release and secretion of the protein.

Minor amendments are made to the claims to correct various typographical errors therein and no new matter is introduced thereby.

II. Outstanding Rejections

Claims 1-3, 6, 10, 15 and 17 stand rejected under 35 U.S.C. § 103(a) as being obvious over Dyrks *et al.* WO 98/13488 in view of Lam *et al.*, WO 00/66615.

Claims 1, 4 and 5 stand rejected under 35 U.S.C. § 103(a) as being obvious over Dyrks *et al.* in view of Lam and in further view of Nandabalan et al., U.S. 6,057,101.

III. Patentability Arguments

Applicants thank the Examiner for the indication that each of dependent claims 7-9, 11-14, 16 and 18-22 are free of the prior art but submit that independent claim 1 and the other

claims (2-6, 10, 15 and 17) that depend therefrom are also free of the prior art and should be allowed.

A. The Rejections of Claims 1-3, 6, 10, 15 and 17 Under 35 USC §103(a) over Dyrks and Lam Should Be Withdrawn.

The rejection of claims 1-3, 6, 10, 15 and 17 under 35 U.S.C. §103(a) as being obvious over Dyrks *et al.* WO 98/13488 in view of Lam *et al.*, WO 00/66615 should be withdrawn because the references do not disclose and would not be combined to arrive at the claimed invention. While each of Dyrks, Lam and the method of the invention include the step of cleaving a fusion protein, Dyrks discloses a method wherein the secretory protein is directly detected. More specifically, the secretory protein of Dyrks is linked via a protease cleavage sequence to a transmembrane anchor sequence. Upon cleavage the secretary protein is released outside of the cell where it is directly detected.

Lam teaches the use of a repressor domain masking the activity of a reporter protein. In the situation where the reporter protein of Lam is a transcription activator, its release triggers inside the cell transcription of a reporter gene or to confer e.g. antibiotic resistance (in case the reporter gene is CAT).

Neither Dyrks nor Lam teaches the claimed method wherein the activity of the secreted protein regulates a transcriptional activation system which controls the expression of the reporter gene, i.e., by a metabolic product of the secreted protein. Hence, the product of an enzymatic reaction is used to trigger transcription instead of detecting the secreted protein as such.

Even if the skilled person had combined the teachings of Dyrks and Lam (and there is no reason why one would) he would not have arrived at the instant invention as none of the references suggest that the reporter protein be regulated by secretase activity, i.e. by a metabolic product of the secreted protein. This "extracellular loop" to a reporter gene screening system is not disclosed in any of the cited documents.

The use by the invention of such an extracellular loop to a reporter gene in a screening system has the technical advantage of providing a quality control for secretion and thus for a functional secretase inhibitor and at the same time provides direct detection and/or survival of

the cells contacted by a secretary inhibitor. As such, the system of the invention has a further advantage that false positive signals due to toxic compounds are omitted, as the readout is not correlated with cell growth. Accordingly, the screening system of the present invention offers a highly reliable screening system.

The methods of the invention also constitute an improvement over prior art systems because they require minimal liquid handling steps. Once the cell suspension has been added to wells containing the test substances, the automated reader simply measures the cell density or a colorimetric or fluorescent signal after defined time intervals. In this manner the inventive methods allow for continuous monitoring.

In contrast, Dyrks discloses analysis of secretase activity based on the release of the polypeptide components which are measured by further assay steps. (See Example 4 which discloses the use of a SEAP assay and page 14 of Dyrks which discloses two variants of SEAP assays involving the addition of a test substance, incubation at elevated temperature and the addition of an assay buffer.

For these reasons the rejection of claims 1-3, 6, 10, 15 and 17 over Dyrks and Lam should be withdrawn.

B. The Rejections of Claims 1, 4 and 5 Under 35 USC §103 in view of Dyrks, Lam and Nandabalan Should Be Withdrawn.

The rejection of claims 1, 4 and 5 under 35 U.S.C. §103(a) as being obvious over Dyrks in view of Lam and in further view of Nandabalan et al., U.S. 6,057,101 should also be withdrawn because independent claim 1 is patentable over Dyrks and Lam for the reasons set out above and because Nandabalan fails to make up for the deficiencies of Dyrks and Lam.

Nandabalan relates to (protein-protein interactions) and would not be combined with those of either Dyrks or Lam because it is directed to a different technical field than that of the invention (secretase-inhibitor assays). The Action argues at page 6 that "the motivation to use negative selection would have come from Nandabalan et al." but there is no motivation to combine Nandabalan with either Dyrks or Lam or to otherwise consider it with respect to the present invention.

While the decision in KSR dispensed with the requirement for a rigid showing of the teaching-suggestion-motivation (TSM) test it still required that any obviousness rejection should be supported by "a clear articulation of the reason(s) why the claimed invention would have been obvious." Thus, even if the rejection of independent claim 1 is sustained (and it should not be), the rejections of claims 4 and 5 should be withdrawn because no articulation has been made as to why it would have been obvious to adopt an aspect of Nandabalan to screen for secretase activities.

CONCLUSION

For the foregoing reasons, it is submitted that each of claims 1-6, 10, 15 and 17 should be allowed in addition to claims 7-9, 11-14, 16 and 18-22 which have previously been indicated to be allowable. Should the Examiner wish to discuss any issues of form or substance, he is invited to contact the undersigned attorney at the number below.

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Respectfully submitted,

By _____

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